UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,383	02/19/2004	Katsuro Tachibana	EKOS.8CP3DV1C4	3583

20995 7590 04/03/2006

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/782,383	TACHIBANA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/158,316.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3/7/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-27 are pending and under consideration in this Office Action.

Information Disclosure Statement

The information disclosure statement filed 2/19/04 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because 37 CFR 1.98(d) indicates that a copy of any patent, publication, pending U.S. application or other information listed in an information disclosure statement is required to be provided, even if the patent, publication, pending U.S. application or other information was previously submitted to, or cited by, the Office in an earlier application, unless the earlier application is properly identified in the information disclosure statement and is relied on for an earlier effective filing date under 35 U.S.C.120. In this case the information disclosure statement indicates that the cited references were present in Application No. 10/246,323, and identifies this application as a parent to the instant application. However, the instant application fails to claim priority to 10/246,323 in either the specification or an application data sheet. Consequently the IDS fails to comply with 37 CFR 1.98 because 10/246,323 is not relied on for an earlier effective filing date under 35 U.S.C.120.

The IDS has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for

purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13, and 15-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and dependents are indefinite because claim 1 recites "the therapeutic composition comprising genetic material" without antecedent basis. It is also unclear what is meant by "a sufficient level of ultrasound energy". The claim does not make clear for what the level of ultrasound energy should be sufficient.

Claim 15 and dependents are indefinite because claim 15 recites "the at least one support member" without antecedent basis.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, and 15-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of delivering a therapeutic composition to a target site comprising "delivering the therapeutic composition comprising genetic material through a catheter to the target site". It is unclear from the claims as written if the recited genetic material is intended to be therapeutic. However, a review of the specification shows that genetic material is intended to be delivered for the purpose of therapy (see e.g. paragraph 2 at page 1; paragraph 131-133 at pages 20 and 21), and in fact, no other purpose for delivering genetic material is disclosed. For that reason, the claims are interpreted as therapeutic methods, and the genetic material is interpreted as intended in the specification, i.e. as a therapeutic. Several types of genetic material are embraced by the claims including "genes carried on expression vectors such as plasmids, phagemids, cosmids, yeast artificial chromosomes (YACs), and defective or "helper" viruses, antigene nucleic acids, both single and double stranded RNA and DNA and analogs thereof, such as phosphorothioate and phosphorodithioate oligodeoxynucleotides" (see paragraph 131 at page 20). As a result, the claims are considered to be drawn broadly to methods of gene and oligonucleotide therapy.

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to

Assess the NIH Investment in Research on Gene Therapy, 1995) taught that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin taught that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) taught that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors stated further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirmed the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). More recently, Romano et al (Stem Cells 18:19-39, 2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (Nature Reviews/Genetics 1: 9199, 11/2000), who noted that delivery vehicles still represented the Achilles heel of gene therapy, and

that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph.

The state of the art with respect to antisense therapies indicates a high level of unpredictability. Crook (In Basic Principles of Antisense Therapeutics, Springer-Verlag, Eds, New York, pgs. 1 and 4), taught that although antisense techniques have progressed rapidly, "the technology remains in its infancy", and the utility of the approach is still debatable (pg. 1, Introduction). Crook pointed out several factors that may influence the biological effect of an antisense oligonucleotide (AODN), including the rate of uptake of the AODN, rate of distribution within the target cell, stability within the target cell, local concentration of the oligonucleotide, and the concentration and stability of the target mRNA (pgs. 1 and 4). Furthermore, Branch (Trends in Biochem. Sci 23: 45-50, 1998) taught that selection of appropriate antisense sequences is difficult because secondary structures of mRNAs *in vivo* frequently restrict access of antisense oligonucleotides to the target sequence (page 45, col. 3. first para., page 48, last para. and page 49). Branch stated, "Since accessibility cannot be predicted, rational design of antisense molecules is not possible" (page 49, col. 2, last para.). Ho and Parkinson (Sem. Drug Discov. 24(2): 187-202, 1997) taught that although antisense therapy is simple in theory, it "has proven to be much more complex in practice. A number of important challenges in the preclinical development of antisense oligonucleotides have been identified, including stability, sequence length, cellular uptake, target sequence selection, appropriate negative controls, oligonucleotide: protein interactions, and cost of manufacture." The authors concluded that "[c]ontinued progress in this arena will

require that many of the preclinical challenges confronting antisense development are satisfactorily resolved." See abstract. Akhtar (J. Antimicrob. Chemother. 38(2): 159-165, 1996) taught that "a healthy degree of concern exists among scientists and administrators as to whether antisense and, to some extent, ribozyme oligonucleotides will ever become useful therapeutic agents." See page 163, column 1, lines 5-14 of first full paragraph. Thus, at the time the invention was made, there was considerable unpredictability in the design of antisense oligonucleotides, their delivery and pharmacodynamics, and most importantly, whether or not they would ultimately have any therapeutic value.

Guidance in the specification regarding gene and oligonucleotide therapy is insufficient in view of the state of the art. The specification at paragraph 133 suggests examples of specific genes that can be used to treat various diseases including for example, adenosine deaminase to treat ADA deficiency; tumor necrosis factor and/or interleukin-2 may be provided to treat advanced cancers; HDL receptor to treat liver disease; and HIV env may to treat HIV infection. However, the specification provides no working example of any method of gene therapy, or even of delivery of genetic material in vivo or in vitro. No guidance is provided as to the site to which any gene therapeutic must be delivered for any therapeutic purpose. No guidance is provided as to how to obtain and maintain therapeutic levels of gene expression.

At the time of the invention, attempts were being made to treat ADA gene deficiency by gene replacement therapy, although at the time of filing no unambiguous success had been reported. In any case, a review of the art indicates that the methods

under investigation focused on gene delivery to white blood cell progenitors. The instant specification provides no guidance as to how one could use the claimed catheter-based methods to delivery to white blood cell progenitors, or to white blood cells. Also, the specification provides no guidance as to what cells should be targeted if not white blood cells or their progenitors. At the time the invention was filed, there were no known methods of treating any liver disease by delivery of genes encoding HDL receptor. Although it is unreasonable to assume that all liver diseases could be treated by HDL receptor gene delivery, the specification provides no guidance as to any specific liver disease that can be treated in this fashion. Also, at the time the invention was filed, and to the present day, there were no known treatments of HIV using env protein. In view of the state of the art at the time of the invention (8/5/98) as discussed above, the level of unpredictability in the art particularly with regard to gene delivery and expression and oligonucleotide delivery and pharmacokinetics, and the limited guidance and lack of working examples in the specification, one of skill in the art could not have practiced therapeutic gene or oligonucleotide delivery as broadly claimed without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the

> applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 14 is rejected under 35 U.S.C. 102(e) as being anticipated by Berg et al (US Patent 6,680,301).

Berg taught a composition comprising the light activated drug AlPcS2a and a ribozyme. See column 12, lines 28-31. Thus Berg anticipates the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Berg et al (US 5,876,989) or Berg et al (WO 96/07432).

The '989 patent is the national phase of the '432 publication. The documents will be discussed with reference to the '989 patent.

Berg taught that nucleic acids such as DNA, RNA, and oligonucleotides could be delivered to cells by photochemical internalization in which cells are contacted with a photoactivatable drug such as $TPPS_4$ or $AlPcS_2$, and the nucleic acid. Berg did not explicitly teach a composition comprising both a nucleic acid and a photactivatable drug.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine a photoactivatable drug in a composition with a nucleic acid in

order to simplify delivery of these molecules to target cells. For example, Berg taught a method in which the toxin gelonin was delivered to cells by photochemical internalization, and in which cells were incubated in a the presence of a composition comprising both gelonin and the photoactivatable drug $TPPS_{2a}$. See column 5, lines 53-56. thus one of ordinary skill in the art seeking to apply the invention to the delivery of nucleic acid molecules, as suggested by Berg, would find motivation to combine the photoactivatable drug and the nucleic acid in a delivery composition.

Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635